REMARKS

Claims 1-17 are pending in the application. Claims 1-17 were examined and stand rejected. Applicants have cancelled Claims 1-17 and submit new Claims 18-29. Applicants present clean new Claims 18-29 pursuant to 37 C.F.R. §1.121 (c)(i) above, with the marked-up claims pursuant to 37 C.F.R. §1.121 (c)(ii) in the following appendix presented herewith. Applicants hereby request further examination and reconsideration of the instant application in view of the foregoing amendments.

CLAIM FOR FOREIGN PRIORITY UNDER 35 U.S.C. §119(b)

The Examiner noted that Applicants had not yet submitted a certified copy of the Estonian patent application to which Applicants claim priority. In response to this observation, Applicants have filed herewith a certified copy of the Estonian priority document filed April 19, 1999 to fulfill the requirements of 35 U.S.C. 119(b) (Tab C).

OBJECTION TO CLAIMS 2-12 UNDER 37 C.F.R. §1.75(C)

The Examiner objected to originally filed Claims 2-12 in which a typographical error led to improper claim dependency. Applicants have cancelled Claims 1-17 and substitute new Claims 18-29. Applicants submit that new Claims 18-29 are free of the defaults detected in originally filed Claims 2-12.

35 U.S.C. §112, FIRST PARAGRAPH REJECTION OF CLAIMS 1-17 WRITTEN DESCRIPTION

The Examiner rejected Claims 1-17 under 35 U.S.C. §112, first paragraph, on the grounds that the specification does not reasonably convey to one skilled in the relevant art that the Applicants had possession of the claimed invention at the time of filing. The Examiner stated on page 3 of the Official Action issued March 30, 2001 that "the specification neither incorporates by reference prior art devices and subsequently teaches how the claimed device is modified . . ." Applicants respectfully traverse this rejection.

The specification discusses conventional and commercially available fluorescence detectors (e.g. GenoSensor™ Vysis, Inc.) and the disadvantages associated with state-of-the-art fluorescence

detectors that analyze microarrays (page 2, paragraph 5). The instant application reports that these prior art detectors possess one or more filters through which light from a xenon bulb passes in order to specifically excite fluorescently – labeled oligonucleotides hybridized to DNA probes bound to a glass support (page 2, paragraph 4). Further, the optical noise resulting from the high density fluorescently – labeled oligonucleotide array and the use of transversing light (exemplified in Figure 1) to excite fluorophores are discussed as disadvantages of conventional detectors. In contrast, Applicants describe the use of total internal reflection, instead of transversing light, to excite fluorophores as advantageous. See a detailed description of Applicants' invention at paragraphs 8-20 and in Figures 1-5. Paragraphs 4 and 5 taken with the disclosure that "The fluorescence detector described here overcomes the before mentioned disadvantages" (page 2, paragraph 6) provide sufficient written description to demonstrate that Applicants were in possession of the invention at the time of filing and even recognized that their invention possessed advantages over the prior art.

The Examiner stated that the specification does not ". . . provide detailed description as to how the claimed device is to be manufactured, assembled, and ultimately utilized" (page 3, Official Action issued March 30, 2001). The invention is an apparatus, or subassembly, to be employed in a fluorescence detector (Figure 5) that directs a light source into a waveguide to cause total internal reflection (Figures 2-4). As to the specification's support for the manufacture and assembly of the claimed invention, Applicants submit that the drawings and text of the application describe adequately to one skilled in the art of optics how the invention can be manufactured and assembled. To utilize the claimed invention, the specification as filed clearly states that the APEX method of nucleotide identification is optimally employed with the invention of the instant application (page 5, paragraph 19). Paragraph 19 describes how one may use the claimed fluorescence detector with the APEX method. Details of this methodology are explained in issued U.S. Patent 6,153,379, but the present application contains sufficient written description to indicate that the inventors had possession of the claimed invention – an instrument that employs total internal reflection to excite and analyze fluorescently – labeled microarrays. The specification concludes that "The presently disclosed invention is distinctly configured to be used with the APEX assay" (page 3, paragraph 7).

35 U.S.C. §112, FIRST PARAGRAPH REJECTION OF CLAIMS 16-17 WRITTEN DESCRIPTION

Although Claims 16 and 17 have been cancelled, new Claims 28 and 29 approximate the same subject matter. Claims 16 and 17, drawn to the method of using APEX with the claimed apparatus for use in a fluorescence detector, have been rejected under 35 U.S.C. §112, first paragraph, on the grounds that this method has not been adequately described. Applicants traverse this rejection and submit that the methods of new Claims 28 and 29 are adequately expressed and supported by the specification, delineating all the steps required to use APEX with the claimed apparatus for use in a fluorescence detector. The claimed apparatus for use in a fluorescence detector is particularly well suited to analyze results from the APEX method of nucleotide identification (page 5, paragraph 19). Because the acronym APEX is well recognized in the art of nucleotide sequence anaysis as well as has been previously described (indeed, previously patented in U.S. Patent 6,153,379), Applicants submit that its identification alone as a method with which to use the claimed invention is adequate.

35 U.S.C. §112, FIRST PARAGRAPH REJECTION OF CLAIMS 1-17 ENABLEMENT

The Examiner has rejected Claims 1-17 under 35 U.S.C. §112, first paragraph, on the grounds that the subject matter was not described in the specification in enough detail to enable one skilled in the art to make and use the invention. In response to the Examiner's rejections, Applicants have cancelled Claims 1-17 and substituted claims 18-29, provided arguments for their acceptance, submitted a Declaration of Dr. Lewis T. Claiborne under Rule 37 C.F.R. §132 (Tab A), and presented the curricula vitae for each of the three inventors (Tab B). The Examiner cites *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) with providing the test applied by the Office to the instant application. Each prong of this test will be addressed below.

The quantity of experimentation necessary – The Examiner contends that the quantity of experimentation needed to make and use the claimed invention is great, on the order of several man-years and then with little, if any, reasonable expectation of success. To make and use the apparatus to be employed in a fluorescence detector of the present invention would not require undue experimentation, given the level of skill in the art, because the specification names and

illustrates the parts of the fluorescence detector, demonstrates the relationship that exists between the parts, and describes the function of each part (Fig. 1-5, pages 4-5, paragraphs 15-18). Furthermore, Lewis T. Claiborne, a person skilled in the art most closely related to the invention, has declared that he believes that the amount of experimentation necessary to make and use the invention in view of the specification is minimal. See Declaration Under 37 C.F.R. §1.132 (page 3, paragraph 7). The biochemical aspect of the invention is described on pages 5-6 in paragraph 19, original Claim 17, and new Claim 29 which is merely the state-or-the-art as disclosed in U.S. Patent 6,153,379. Even assuming, *arguendo*, that experimentation is necessary to make and use the claimed invention of the instant application, the fact that experimentation may be complex does not necessarily make it undue, if the art is typically engaged in such experimentation. *In re Certain Limited – Charge Cell Culture Microcarriers*, 221 USPQ 1165 (U.S. Int'l Trade Comn. 1983). The industrial arts touched by the invention of the application include physical optics and biochemistry, two fields where some experimentation is expected. For these reasons, Applicants submit that adequate evidence has been presented to show that experimentation, if required to make and use the claimed invention, is not undue.

The amount of direction or guidance provided – The Examiner stated that the amount of guidance provided to make and use the claimed invention, be it in regard to the claimed device or to the methods, is most limiting. Applicants submit that because the specification names and illustrates the parts of the apparatus to be used in a fluorescence detector, demonstrates the relationship that exists between the parts, and describes the function of each part (Fig. 1-5, pages 4-5, paragraphs 15-18), the amount of direction is adequate. Furthermore, Lewis T. Claiborne has declared that the amount of direction provided in the specification is adequate for a person skilled in the art to make and use the claimed invention in his Declaration Under 37 C.F.R. §1.132 (page 3, paragraph 7). The biochemical aspect of the invention is described on pages 5-6 in paragraph 19, Claim 17, and new Claim 29, and merely represents the state-of-the-art. For these reasons, Applicants submit that adequate evidence has been presented that the specification contains sufficient direction and guidance to permit one skilled in the art to make and use the invention as claimed.

The presence or absence of working examples – The Examiner stated that there are no working examples for the manufacture or the use of the claimed device. In the declaration of Lewis

T. Claiborne accompanying this amendment, it is opined by one skilled in the relevant art that the specification of the instant application together with the drawings exemplify a working example of the claimed invention. See Declaration Under 37 C.F.R. §1.132 (page 3, paragraph 7). Even assuming, arguendo, that the specification does not support a working example, working examples are not necessary for enablement if the invention is disclosed in a manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 422 F2d. 904, 908, 164 USPQ 642, 645 (CCPA, 1970).

The nature of the invention – The Examiner stated that the invention relates to the disciplines of physiology and chemistry, which are highly unpredictable. Applicants disagree with the Examiner's assessment that the apparatus to be used in a fluorescence detector of the instant invention is physiological. Instead, the disciplines of the instant invention is physical, involving most heavily the field of optics. The specification states that the invention of the instant application is ". . . particularly well suited for detecting and analyzing data generated with the APEX method of sequence identification" (page 5, paragraph 19). Furthermore, the biochemical aspect of APEX is extensively described particularly in paragraph 19 in the instant application and in U.S. Patent 6,153,379, which describes the state-of-the-art. Even if the nature of the invention is complex, the optical principles on which the fluorescence detector as described in the instant application are basic (pages 3 and 4 in paragraph 8). The Declaration Under 37 C.F.R. §1.132 of Lewis T. Claiborne supports Applicants' arguments: "Because the claimed fluorescence detector is based on accepted physical and optical principles, I believe that the nature of the invention, although complex, is not unpredictable" (page 3, paragraph 7).

The state of the prior art – The Examiner identified numerous art-recognized problems for hybridization based nucleic acid assays. The claims of the current application seek merely to cover the use of the apparatus to be used in a fluorescence detector to analyze the results of the APEX method. Additionally, as mentioned above, APEX has been extensively described and details regarding the assay can be found in U.S. Patent 6,153,379 which explains how to overcome these art-recognized problems. Applicants submit that due to the prevalence and availability of details describing APEX, they are not required to repeat information already known in the art.

The relative skill of those in the art – The Examiner determined that the relative skill of those in the art is high, an example of such a person being a scientist with a Ph.D. in biochemistry. Applicants, however, contend that the relevant person skilled in the art is one familiar with fluorescence detectors and their use. Applicants submit that the skilled person in the art is educated in physics, preferably with a background in optics. Lewis T. Claiborne, an independent consultant with extensive experience in physical optics, has declared that the relative skill in the art most closely associated with the claimed fluorescence detector is on par with those educated in the field of physics or particularly in physical optics. See Declaration Under 37 C.F.R. §1.132 (page 3, paragraph 6).

In addition to Lewis Claiborne's declaration, the Applicants submit the curricula vitae for the three inventors, Ants Kurg, Andres Metspalu, and Yevgeny Berik, attached to this amendment behind Tab B. Ants Kurg has a Ph.D. in Molecular Biology, Andres Metspalu has an M.D. and a Ph.D. in Molecular Biology, and Yevgeny Berik has a Ph.D. in Quantum Electronics. The collaboration of these three scientists, with their diverse complement of backgrounds, resulted in the invention of the instant application. Dr. Berik's participation in the conception of the invention is evidence that a background in physical science is required for a pserson skilled in the art which which the claimed invention is most closely associated. The Declaration Under 37 C.F.R. §1.132, coupled with the physical optics background of one of the inventors, substantiates Applicants' belief that a person skilled in the art of the invention of the fluorescence detector is not a Ph.D. biochemist, as the Examiner suggested, but a physicist.

The breadth of scope of the claims – The Examiner stated that the claims are sufficiently broad such that they encompass genera of devices and methods of analyzing nucleic acid sequences. In the absence of art to support what this "genera of devices" might be, Applicants cannot respond completely. Applicants can only reiterate that the specification names the parts of the apparatus to be used in the fluorescence detector, demonstrates the relationship that exists between the parts, and describes the function of each part (Fig. 1-5, pages 4-5, paragraphs 15-18). Additionally, new claims recite an apparatus for use in a fluorescence detector wherein the light source causes total internal reflection. The biochemical aspect of the invention, that is the use of the claimed apparatus for a fluorescence detector, is described in on pages 5-6 in paragraph 19 and in original Claim 17 (now Claim 29).

In summary, Applicants submit that to make and use the claimed invention undue experimentation is not required, that the amount of direction is adequate, that the absence of a working example does not render the specification non-enabling, that the nature of the invention is based on sound optical principles and is therefore not highly unpredictable, that the state of the prior art of nucleic acid assays is not needed in the specification, that the relative skill of those in the art of fluorescence detection is based in physical optics, and that the breadth of scope of the claims appears to be supported by the specification in absence of evidence to the contrary.

35 U.S.C. §112, SECOND PARAGRAPH REJECTION OF CLAIMS 1-17 INDEFINITENESS

The Examiner rejected Claims 1-17 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard is their invention. Applicants have cancelled Claims 1-17 in favor of new Claims 18-29. Applicants submit that new Claims 18-29 are free of the faults found in original Claims 1-17. In all other respects, the rejection is traversed.

CONCLUSION

For reasons delineated above, Applicants respectfully request the consideration of all pending claims, and favorable action on the same. If additional funds are required for this response to be considered, please deduct said amount from the Sidley Austin Brown & Wood Deposit Account 18-1260. Likewise, if overpayment has been instructed, please refund Deposit Account 18-1260.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

1. (Cancelled)
2. (Cancelled)
3. (Cancelled)
4. (Cancelled)
5. (Cancelled)
6. (Cancelled)
7. (Cancelled)
8. (Cancelled)
9. (Cancelled)
10. (Cancelled)
11. (Cancelled)
12. (Cancelled)
13. (Cancelled)
14. (Cancelled)
15 (Cancelled)
16. (Cancelled)
17. (Cancelled)

18. (New Claim) A device for receiving a light beam from a light source used in the analysis of biological molecules linked to a fluorophore, wherein said biological molecules are affixed to a top surface of a waveguide support capable of supporting total internal reflection and further comprising a bottom surface, and at least one edge surface, said device comprising means for directing said light beam into said edge of said waveguide support.

19. (New Claim) The device of claim 18, further comprising a transparent hexahedron to direct said light beam into said edge of said waveguide support to effect total internal reflection, placed between said light source and said waveguide support, wherein said

transparent hexahedron occupies the same plane as said light beam and revolves around an axis perpendicular to said light beam.

20. (New Claim) The device of claim 1, further comprising an optical wedge to direct said light beam into said edge of said waveguide support to effect total internal reflection, wherein said optical wedge is placed between said light source and said waveguide support and revolves around an axis approximating said light beam.

21. (New Claim) The device of claim 1, further comprising a cylindrical lens to direct said light beam into said edge of said waveguide support to effect total internal reflection, wherein said cylindrical lens is placed between said light source and said waveguide support for focusing said light beam into a shape smaller than said edge of said waveguide support, and wherein said cylindrical lens moves perpendicular to the plane of said light beam.

22. (New Claim) The device of claim 1, wherein said means comprises a mirror to direct said light beam into said edge of said waveguide support to effect total internal reflection, wherein said mirror is placed adjacent to said waveguide.

23. (New Claim) The device of claim 1, further comprising a diffraction grating to selectively allow light of a specific wavelength to excite said fluorophore, wherein said diffraction grating is placed between said light source and said waveguide support.

24. (New Claim) The device of claim 1, further comprising an optical prism to direct said light beam into said edge of said waveguide support to effect total internal reflection, wherein said optical prism is placed adjacent to said waveguide support.

25. (New Claim) The device of claim 1, further comprising a transparent liquid to direct said light beam into said edge of said waveguide support to effect total internal reflection, wherein said transparent liquid is placed between said waveguide support and said optical prism and possesses a refractive index about equal to the refractive indices possessed by said waveguide support and said optical prism.

26. (New Claim) The device of claim 1, further comprising bandpass filters to separate emission spectra, wherein said bandpass filters are placed between said waveguide support and said charge – coupled device.

27. (New Claim) A device for receiving a light beam from a light source used in the excitation, detection, and analysis of biological molecules linked to a fluorophore, wherein said biological molecules are affixed to a top surface of a waveguide support further comprising a bottom surface, and at least one edge surface, said device comprising:

a) a transparent hexahedron to direct said light beam into said edge of said waveguide support to cause effect internal reflection, wherein said transparent hexahedron is adjacent to said light source, occupies the same plane as said light beam, and revolves around an axis perpendicular to said light beam;

b) an optical wedge to direct said light beam into said edge of said waveguide support to effect total internal reflection, wherein said optical wedge is adjacent to said transparent hexahedron and revolves around an axis approximating said light beam;

c) a cylindrical lens to direct said light beam into said edge of said waveguide support to effect total internal reflection, wherein said cylindrical lens is adjacent to said optical wedge, focuses said light beam into a shape smaller than said edge of said waveguide support, and moves perpendicular to the plane of the light beam; and

d) a mirror to direct said light beam into said edge of said waveguide support to cause total internal reflection, wherein said mirror is adjacent to said cylindrical lens.

28. (New Claim) A method for detecting and analyzing a specific nucleic acid sequence comprising:

a) inserting a waveguide support into a fluorescence detector, said waveguide support being spatially situated between a light source and a charge – coupled device in said fluorescence detector, wherein oligonucleotides of known sequences are fixed to said waveguide support at known positions, wherein at least one said oligonucleotide possesses at least one fluorescent nucleotide;

b) exciting said fluorescent nucleotide by directing said light source to said waveguide support to cause total internal reflection;

c) detecting emission from said fluorescent nucleotide with said charge – coupled device; and

d) analyzing said emission on a personal computer.

29. (New Claim) A method of analyzing the sequence of a polynucleotide of interest, comprising the steps of:

a) attaching an array of oligonucleotide primers having known sequences to a solid support at known locations, wherein said solid support may act as a waveguide;

b) hybridizing said polynucleotide of interest to the array of oligonucleotide primers to generate double stranded oligonucleotides;

c) subjecting the double stranded oligonucleotides to a sequence specific single base polymerization reaction to extend the annealed primers by the addition of a fluorescently – labeled terminating nucleotide, wherein said primers may be extended by any fluorescently – labeled terminating nucleotide which is complimentary to the polynucleotide of interest;

d) removing the polynucleotide of interest from the array of oligonucleotide primers;

e) inserting said support into a fluorescence detector, wherein said support is spatially situated between a light source and a charge – coupled device in said fluorescence detector;

f) exciting said fluorescent nucleotide by directing said light source into said support to cause total internal reflection;

g) detecting emission from said fluorescent nucleotide with said charge – coupled device; and

h) analyzing said emission on a personal computer.